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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/902,615	07/10/2001	Avi Ashkenazi	10466-65	9850

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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	14

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 39-44 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 39-44 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ [illegible]
[illegible]
Notice of Draftsperson's Patent Drawing Review [illegible]
__ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-404-496-40517

Part III: Detailed Office Action

Claims 39-44 are pending and under consideration.

The pending claims are directed to antibodies that bind PRO326, SEQ ID NO: 294, which is encoded by SEQ ID NO: 293, DNA 37140-1234, deposited as ATCC 209489.

Priority determination:

Based upon the lack of utility and enablement of the claimed subject matter, priority is granted only to the instant filing date, 7/17/01.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 7/17/01 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 7/17/01.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The information disclosure statement, paper number 7, has been considered.

Double Patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ

761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 39-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/909088. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to antibodies that bind PRO335, which is 100% identical to SEQ ID NO: 294 from residue 20 to the terminus. Accordingly, PRO326 and PRO335 appear to differ only in their signal sequences, and the claims are coextensive as antibodies that bind one would largely also bind the other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Objections and Rejections under 35 U.S.C. §101 and 112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification discloses a protein designated PRO326, and nucleic acid encoding such.

of the leucine rich repeat superfamily. At page 110 it is stated that PRO335, 331 and 326 polypeptides "are related to LIG-1 and possess the biological functions of this family." However, what specific biological functions PRO326 possesses that are in common with LIG-1, and what uses that would indicate for PRO326 are not indicated. At page 138, it is stated "Uses for PRO335, PRO331 or PRO326 including uses in competitive assays with LIG-1, ALS and decorin *to determine their relative activities* (emphasis added)." Because there are no utilities asserted for the claimed antibodies, the implicit utility therefore is to assay or isolate the protein to which the antibodies bind. Accordingly, to have utility, the protein to which the antibodies bind must also have utility, that is, the utility of the antibodies flows from that of the protein.

Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein, the claimed invention is incomplete. Merely using the protein to determine the properties thereof does not constitute a patentable utility.

It is further noted that PRO326 is disclosed as having given positive results in three assays. The first is found at pages 208-209 of the specification, and is described as a mixed lymphocyte reaction. The specification states that "any value greater than control indicates a stimulatory effect for the test protein." This assay is not considered to impart utility to the protein PRO326, nor to the nucleic acids that encode it. The reason for this determination is that no results are presented, and

standard in the scientific community. It is well accepted in experimental science that, in order for a result to be positive, it must be *significantly* different from the control value, not "any value greater" as reported in the specification. Accordingly, the tacit assertion that PRO326 has a positive reaction in a mixed lymphocyte assay, and could therefore be used 'as a stimulator of the proliferation of stimulated T-lymphocytes" does not meet the requirements of 35 U.S.C. § 101, as the assertion of utility would not be considered substantial by a person of ordinary skill in the art.

The second assay in which PRO326 was stated to give positive results is found at pages 210-211, the skin vascular permeability assay (Assay 64). Presumably a positive reaction indicates that a measurable blemish was observed (though this is not clearly stated), and then biopsied, and one or more types of inflammatory cells were observed in the biopsy. This assay is not considered to be indicative of utility for PRO326, because it is merely what is commonly known as an immediate type hypersensitivity assay, and does not inform as to what the protein could be used for, especially in the absence of any information as to what *particular* cell types were observed in the biopsy. Thus, it is not clear what type of immune response was stimulated, nor what utility would stem from such. Again, the person of ordinary skill in the art would not find that this assay constitutes a specific, substantial and credible assertion of utility.

Finally, at pages 218-222 (Example 91), the specification discloses an in vitro antitumor assay (assay 161). The specification discloses, in Example 91, that the PRO326 protein was active, causing at least 50% growth inhibition, against four of the 60 cell lines of the National Cancer Institute (NCI) anticancer drug discovery screen (the NCI panel). The asserted utility of nucleic acids encoding the claimed PRO326 protein as a possible chemotherapeutic agent is not considered to be specific, substantial and credible, for the following reasons: Monks et al., Journal of the National Cancer Institute, vol. 83(11):757-766, cited by applicants at page 218, disclose and explain the screen itself, including how the screen is performed, and what cell lines are used. The 60 cell lines are independent isolates representing seven distinct types of cancer, namely lung cancer (13 cell lines), renal cancer (9 cell lines), colon cancer (9 cell lines), melanoma (9 cell lines), CNS cancer [illegible]

218-222, discloses that PRO326 tested positive in 4 cell lines, representing three CNS, and one NSCL cancers. Based on disclosed results for other PRO polypeptides, other cell lines tested included a variety of cancer cell lines, including breast cancer cell lines. As the Monks et al. disclosure does not disclose any breast cancer cell lines as being in the panel, it is not clear exactly *which* "NCI panel" was used.. It is also noted that the composition of the NCI panel is not static, as Shi et al., referenced below, disclose a different set of 60 cell lines than that disclosed by Monks et al. It cannot be determined how many CNS and NCSL cancer cell lines were present in the panel used. Therefore, there is no discernable pattern of activity, i.e. the protein does not appear to be active against any particular type of cancer, nor against anything approaching a majority of the cell lines for any given type of cancer. Since PRO326 does not appear to give significant results when tested against the NCI panel, the implicit assertion of utility for the protein (and by extension nucleic acids encoding such) as an anti-cancer agent is not specific, as such could be asserted for almost any protein, which would be toxic for one or more cell types at some concentration. Further, the implicit assertion of anticancer activity is not substantial. Johnson et al. (Brit. J. Cancer 84(10):1424-1431), in an article entitled "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials", state, with regard to the NCI panel that "Agents selected on the basis of potency, selective activity against a particular disease category, and/or differential activity against a few specific cell lines were then evaluated against a small number of sensitive human tumours in the nude mouse xenograft model (citations omitted) as a basis for selecting compounds for further preclinical development. Owing to the large numbers of molecules emerging from the in vitro screen as candidates for xenograft testing, in 1995 this development path was further modified to include a hollow fibre (HF) assay, activity in which was a prerequisite for study in classical xenograft models" (page 1424, second column). Thus, the initial screen against the 60 cell lines of the NCI panel is not considered by the art to be predictive of *in vivo* activity against tumors, and, as characterized by Johnson et al., such is merely the first of a three-part protocol for identification of agents to be tested in vivo. Further, Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-

informative, activity *patterns* across the 60 cell lines can provide incisive information on the mechanisms of action of screened compounds...." (abstract). The paper, drawn to methods of mining and visualizing the large amounts of data generated by the NCI panel, further states that relative activity levels distinguish better among the tested cell lines than do the GI_{50} activity patterns, and that "The mean zero preprocessing procedure seemed to eliminate the noninformative "inherent" cytotoxicity, thus brining out the informational differential cell responses (p. 377, end of first column). Thus, Shi et al. indicates that the art does not consider the raw GI_{50} data are insufficient to identify compounds that are likely to be antitumor candidates to be tested further. Accordingly, the implicit assertion of utility as an anti-cancer agent is not substantial, as the art does not support that mere identification of 50% killing of 4 of the 60 NCI panel cell lines would be predictive of anti-tumor activity, and thus would not constitute a substantial and credible utility for PRO326 and by extension nucleic acids encoding such.

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to antibodies that bind a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein or the polynucleotides encoding it, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 states that the claimed antibody "binds" the polypeptide of SEQ ID NO:294, whereas claim 44 is drawn to an antibody that "specifically binds" to the same polypeptide. It is not clear how the scope of those two terms differs, nor hence what the metes and bounds of the claims are.

Claim 42 is indefinite because an antibody cannot be a fragment of itself.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of [illegible] of 35 U.S.C. 112 that [illegible]

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 39-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Wu et al., U.S. Patent Number 6,046,030.

U.S. Patent Number 6,046,030 teaches a protein of SEQ ID NO: 5, having 50% identity to residues 1-1083 of SEQ ID NO: 294, and SEQ ID NO: 2, having 49.8% identity to residues 32-1036 of SEQ ID NO: 294. 21 lines 59 to column 22 line 17. Labeled antibodies are disclosed at column 23, lines 42-53. Because of the relatedness of Wu's sequences to those of SEQ ID NO: 294, Wu's antibodies would reasonably be expected to meet the limitations of the rejected claims.

Claims 39-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang et al., U.S. Patent Number 6,426,072.

U.S. Patent Number 6,426,072 teaches SEQ ID NO: 4, which has 74.8% identity to residues 608-737 of SEQ ID NO: 294.

Antibodies to the proteins, including single chain and humanized antibodies, are disclosed at column 50. Immunoassays using labeled antibodies are disclosed at col. 25. Because of the relatedness of Wang's sequences to those of SEQ ID NO: 294, Wang's antibodies would reasonably be expected to meet the limitations of the rejected claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A search of the protein sequence databases revealed the following prior art:

Locus	Date	Author	Identity to SEQ ID NO:294
Q9D332	6/1/01	J. Kawai et al.	86% to residues 378-1119
O94898	5/1/99	T. Nagase et al.	58.4% to residues 47-1036
P70193	2/1/97	Y. Suzuki et al.	50% to residues 1-1083

Claims 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. or Nagase et al. or Suzuki et al., any of the three in view of in view of Sibson et al., WO94/01548.

The three primary references disclose proteins with varying amounts of identity to SEQ ID NO: 294, as summarized above. Each is disclosed as being encoded by an isolated cDNA. The primary references do not specifically disclose production of antibodies to the proteins.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Sibson teaches the use of such antibodies to detect proteins to which they bind, which would indicate labeling of the antibodies.

It would have been obvious to the person of ordinary skill in the art at the time the invention

was made make antibodies to any of the proteins disclosed by Kawai et al. or Nagase et al. or Suzuki et al. as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above. The production of polyclonal, chimeric, single chain, and labeled antibodies, as well as of hybridoma cells that produce antibodies is further considered obvious over Kawai et al. or Nagase et al. or Suzuki et al. in view of Sibson et al., as all are notoriously old and well known in the art, and would be immediately envisaged by the person of ordinary skill in the art upon reading the Sibson et al. disclosure.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector, Ph.D.
Primary Examiner

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4/21/03